Solubility of Tobramycin in Methanol, Ethanol, Dimethyl Sulfoxide, and *N*,*N*-Dimethylformamide

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The solubilities of tobramycin in methanol, ethanol, dimethyl sulfoxide, and *N*,*N*-dimethylformamide were measured at temperatures from (283.15 to 318.15) K by a synthetic method at atmospheric pressure. The experimental solubilities were correlated with the modified Apelblat equation which provided an accurate mathematical representation of the experimental data.

Introduction

Tobramycin (4-*O*-(3-amino-3-deoxy-a-D-glucopyranosyl)-2-deoxy-6-*O*-(2,6-diamino-2,3,6-trideoxy-a-D-ribohexopyranosyl)-L-streptamine; CAS No. 32986-56-4), produced by the bacterium *Streptomyces tenebrarius*, is a broad-spectrum aminoglycosidic antibiotic and used almost exclusively in the treatment of Gram-negative bacteria.[1,2] Crystallization plays an important role in the tobramycin production process, and the solubilities of tobramycin in different solvents are crucial to optimize the crystallization process.[3] However, no reports concerning solubility of tobramycin in pure organic solvent have been published. In this work, solubilities of tobramycin in pure organic solvent over a temperature range have been measured by a synthetic method.

Experimental Section

Materials. All the chemicals were of analytical reagent grade. A solid sample of tobramycin with a minimum mass fraction of 97.5 % was crystallized in the laboratory which was supplied by the Chongqing Daxin Pharmaceutical Co., Ltd. (Chongqing, China). Tobramycin was the same as the sample used in a previous experiment which determined the solubility of tobramycin in binary water−ethanol solvent.[4] The solute sample was dried to constant weight in vacuum at 338 K and then stored in a desiccator. Methanol, ethanol, dimethyl sulfoxide, and *N*,*N*-dimethylformamide were from the Tianjin Kewei Chemical Company (Tianjin, China).

Procedure. The solubility was measured by a synthetic method. At the beginning, the mass of the solute and the solvent was determined with an electronic analytical balance (type AL204, Mettler Toledo) with an uncertainty of ± 0.1 mg. The solvent was loaded into the jacketed vessel which was kept at the desired temperature by circulating water from a constant-temperature bath (type 501A, China), and the temperature of the circulated water was controlled within ± 0.2 K of the desired temperature. The solution was stirred by an electric magnetic stirrer, and a microthermometer was used to determine the temperature of the system; the thermometer had an uncertainty of 0.05 K. All solubility experiments were conducted three times to check the repeatability in this work, and the repeatability evaluated by mean relative deviation was less than 3 %.

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Table 1. Experimental Solubilities (x^{exptl}) and the Relative Deviation (δ) of Tobramycin in Different Organic Solvents[a]

T/K	$10^3\ x^{exptl}$	100δ	*T*/K	$10^3\ x^{exptl}$	100δ
		Methanol			
288.15	0.1288	28.59	303.15	0.2845	4.43
293.15	0.1329	2.99	308.15	0.4328	0.19
298.15	0.1888	7.15	313.15	0.6349	0.90
		Ethanol			
283.15	0.4358	13.66	298.15	1.1444	4.55
288.15	0.5564	0.20	303.15	1.9115	9.27
293.15	0.7083	15.73	308.15	2.4295	2.78
		Dimethyl Sulfoxide			
294.15	12.45	1.99	308.15	23.61	3.46
298.15	14.03	4.14	313.15	28.20	0.60
303.15	18.04	1.26	318.15	35.13	0.34
		N,*N*-Dimethylformamide			
293.15	0.1443	20.76	308.15	0.3935	6.13
298.15	0.1810	1.85	313.15	0.6625	4.57
303.15	0.2495	9.66	318.15	0.9418	0.79

[a] $\delta = |(x_i^{exptl} - x_i^{calcd})/(x_i^{exptl})|$.

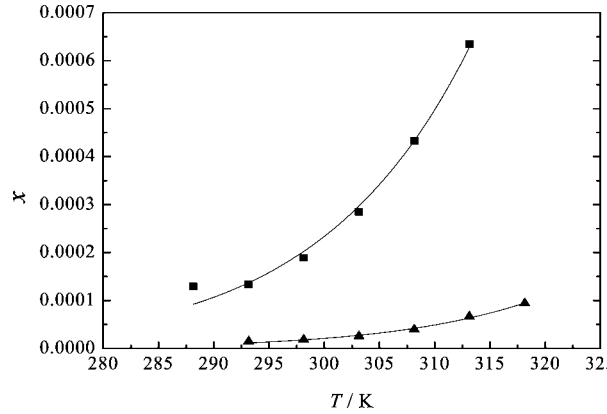

Figure 1. Mole fraction solubility of tobramycin in different organic solvents at different temperatures: ▲, methanol; ■, *N*,*N*-dimethylformamide.

Results and Discussion

The solubility data of tobramycin in pure methanol, ethanol, dimethyl sulfoxide, and *N*,*N*-dimethylformamide at different temperature are presented in Table 1. To show the difference of solubility in those solvents apparently, solubilities are presented in Figure 1 and Figure 2, respectively.

The experimental solubilities were correlated with the modified Apelblat equation[5,6]

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$$\ln(x) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (1)$$

where x is the mole fraction solubility; T is the absolute temperature; and A, B, and C are the parameters of the equation. The calculated relative deviation of tobramycin is also given in Table 1. The relative deviation is defined as

$$\delta = \left| \frac{x_i^{\mathrm{exptl}} - x_i^{\mathrm{calcd}}}{x_i^{\mathrm{exptl}}} \right| \quad (2)$$

where x_i^{calcd} represents the solubility calculated from eq 1 and x_i^{exptl} represents the experimental solubility. The values of A, B, and C and the root-mean-square deviations (RMSDs) are listed in Table 2. The rmsd of the mole diffraction is defined as

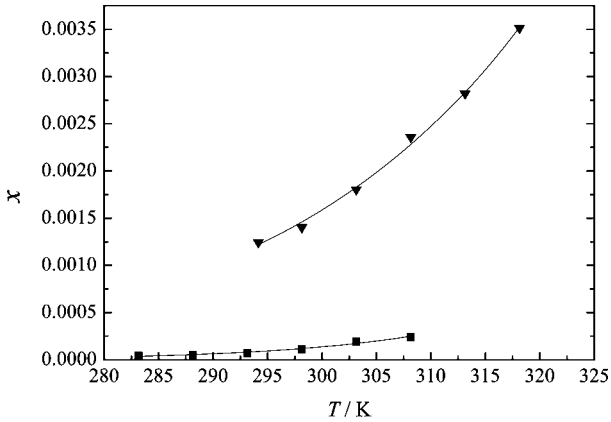

Figure 2. Mole fraction solubility of tobramycin in different organic solvents at different temperatures: ■, ethanol; ▼, dimethyl sulfoxide.

Table 2. Parameters of the Apelblat Equation for Tobramycin in Different Solvents

solvent	A	B	C	10^5 rmsd
methanol	−143.0299	128.4083	23.5351	1.706
ethanol	−118.5815	−789.8889	19.6925	0.954
dimethyl sulfoxide	−121.9972	1746.8454	19.2379	4.397
N,*N*-dimethylformamide	−117.0481	−1873.3156	19.7264	0.225

$$\mathrm{RMSD} = \left[\frac{\sum_{i=1}^{N} \left(x_i^{\mathrm{exptl}} - x_i^{\mathrm{calcd}}\right)^2}{N} \right]^{1/2} \quad (3)$$

where N is the number of experimental points.

Combining the values listed in Table 1 with fitting curves shown in Figure 1 and Figure 2, it can be seen that the calculated solubility shows good agreement with the experimental data. We can draw the following conclusions: (1) The solubility of tobramycin in pure methanol, ethanol, dimethyl sulfoxide, and *N*,*N*-dimethylformamide increases with increasing temperature. (2) The solubility data show that the trend of solubility in different solvents is: $w_{\mathrm{dimethyl\ sulfoxide}} \gg w_{\mathrm{ethanol}} > w_{N,N\text{-dimethylformamide}} > w_{\mathrm{methanol}}$. (3) The temperature dependence of tobramycin solubility in different solvents can be well correlated by the modified Apelblat equations, and the calculated solubilities show good agreement with the experimental values.

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